IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Cope et al.	Art Unit:	1652
Application No.:	10/047,253	Examiner:	Y.D. Pak
Filed:	January 14, 2002	Confirmation No.:	6270
Title:	REGULATION OF TARGET PROTEIN ACTIVITY THROUGH MODIFIER PROTEINS		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

DECLARATION UNDER 37 C.F.R. § 1.132

I, Dr. Craig M. Crews, declare and state that:

1. I am an Associate Professor of Molecular, Cellular, and Developmental Biology at Yale University, New Haven, Connecticut. My scientific research and publications encompass biological mechanisms of proteasome-catalyzed degradation of ubiquinated proteins. My Curricular Vitae is attached as Exhibit A.

2. I am familiar with the subject matter of U.S. Patent Application Serial No. 10/047,253.

3. I understand that the Examiner has rejected the various claims for allegedly not being described in the application as filed, or not providing one skilled in the art to make or use the invention as claimed. In particular, the Examiner has alleged that "any" modifier and target protein is claimed, although only a few are described in the specification (pages 8-15 of the Office Action).

4. The claimed invention is directed to a method of identifying agents which affect Rpn11 or AMSH isopeptidase activity. The method involves detecting the change in Rpn11 or AMSH isopeptidase activity when a test agent is combined with a specific Rpn11 or

AMSH polypeptide in the presence of a modifier and target protein. The specific Rpn11 or AMSH polypeptides are described in the application as discussed above, for example, pages 10-11 and FIG2. Example 1 of the specification describes that the modifier and target proteins are substrates for Rpn11 or AMSH and do not limit the assay, which measures isopeptidase activity of a known or unknown agent. That is, any modifier protein (e.g., ubiquitin) can be used so long as it is a substrate of Rpn11 or AMSH, and Rpn11 and AMSH are capable of cleaving the modifier protein from the associated target protein, in the presence or absence the known or unknown agent (e.g., epoxomicin). Hence, any target protein (e.g., Sic1) can also be used so long as it associates with the modifier protein, and is capable of being cleaved by Rpn11 or AMSH as described in the application. Thus, it is the use of the specific Rpn11 or AMSH polypeptides in the claimed method which is the invention.

5. I declare that all statements made herein of my own knowledge is true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 6/7/06

Craig M. Crews, Ph.D.

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EXHIBIT A

CURRICULUM VITAE

NAME **CRAIG MARTIN CREWS**

EDUCATION AND WORK EXPERIENCE

1982-1986	**B.A., Chemistry,** (minor in Biology), University of Virginia
1986-1987	**DAAD Fellow,** Universität Tübingen, Germany
1987-1993	**Ph.D., Biochemistry,** Department of Biochemistry & Mol. Biology, Harvard University, with Dr. R.L. Erikson
1993-1995	**Postdoctoral Fellow,** Dept. of Chemistry, Harvard University, with Dr. S.L. Schreiber
1995-2000	**Assistant Professor,** Yale University, Dept. of Mol., Cell, &. Dev. Biology
1998-2000	**Assistant Professor,** Yale School of Medicine, Dept. of Pharmacology
2000-	**Associate Professor,** Yale School of Medicine, Dept. of Pharmacology
2000-	**Associate Professor,** Yale University, Dept. of Mol., Cell, &. Dev. Biology *(tenured in 2001)*
2001-	**Associate Professor,** Yale University, Dept. of Chemistry

HONORS AND AWARDS

1986-1987	**DAAD Research Fellowship** for Graduate Research, (German Acad. Exchange Service)
1993	**Damon Runyon Fellowship,** *-declined*
1993	**American Cancer Society Fellowship,** *-declined*
1993-1995	**Cancer Research Institute Fellowship**
1996-1999	**Burroughs Wellcome Fund New Investigator Award**
1996-1999	**Donaghue Foundation New Investigator Award**
1996-1998	**CaPCURE Research Awards** (Assoc. for the Cure of Cancer of the Prostate)
1999	**Arthur Greer Memorial Prize** for Outstanding Junior Faculty Member in the Social or Natural Sciences
1999-2000	**Junior Faculty Fellowship**
2001-	**Editorial Board,** *Molecular and Cellular Proteomics*
2001-	**Editorial Board,** *Faculty of 1000*
2002-	**Editorial Board,** *Chemistry & Biology*
2005-	**Editorial Board,** *Molecular Biosystems*
2006-	**Bessel Research Award,** Humboldt Foundation, Germany

MEMBERSHIPS/AFFILIATIONS

1993-1995	**Member,** Harvard Board of Biochemistry Tutors
1995-	**Fellow** of Pierson College, Yale University
1995-	**Member,** Yale Comprehensive Cancer Center

TEACHING EXPERIENCE

1) 1995-2002; 2004- **Lecturer** (and **Course Director**, 1997) in **Cell Biology (MCDB205b)**- a lecture course introducing students to the concepts and experimental basis of modern cell biology (attendance 120 undergraduate students).

2) 1996-2002 **Course Director in Advanced Seminar in Cell Biology (MCDB692a)**- an advanced seminar course for graduate students to explore and critique experimental design and strategies (attendance: 23 graduate students).

3) 2000-2002 **Course Director in Mechanisms of Signal Transduction (MCDB482a)**- an advanced seminar course for upper level undergraduates focusing on data interpretation using the mitogenic signal transduction primary literature. (attendance: 14 undergraduate students).

4) 1996-present **Lecturer in Pharmacology II: Interfering Selectively (Pharm 504b)** - an advanced seminar course for graduate students that focuses on the fundamentals of modern pharmacology.

5) 1997-present **Lecturer in Current Topics in Cancer and Viral Therapies (Pharm 518b)** - contemporary subjects in experimental therapeutic design taught to graduate students and postdoctoral Fellows.

6) 1997-2000, 2005 **Discussant/Lecturer in Perspectives on Science (SCIE198a)**- a lecture and discussion course that presents a broad range of scientific topics to selected students in their freshman year. (attendance: 40 undergraduates).

7) 2004- **Lecturer in Cell Biology MCDB 602/603**- a graduate level lecture and seminar course focusing on cell biology (attendance: 70)

RESEARCH GRANTS AWARDED

Federal

1996 **Burroughs Wellcome Fund** *Exploring the Pharmaceutical Potential of PKC Isozyme Regulation using Combinatorial Chemistry*
1996 **CaPCURE** Research Support *Development of Novel Anti-angiogenic Compounds* (Assoc. for the Cure of Cancer of the Prostate)
1996 **The Tobacco Research Council** *Molecular Analysis of Didemnin B Binding Proteins*
1997 **NIH R01** GM62120-09 *Natural Product Mode of Action Studies*
1997 **NIH R21** HG01703-01 *Finding Protein Ligands with a Multiplex 3 Hybrid System*
1997 **U.S. Army** (Defense/University Research Instrumentation Program) 37296-RIP (Support for purchase of an automated Multiple Organic Synthesizer)
1998 **CaPCURE** Research Support *Development of Novel Anti-angiogenic Compounds* (Assoc. for the Cure of Cancer of the Prostate) (Renewal for second year)
1999 **NIH R01** CA83049-06A1 *MetAP2 Knockout Mice: Angiostatic Drug Target Validation*

1999 **CaPCURE** Research Support *Development of a Novel Class of Protein-Inhibiting Therapeutics for Prostate Cancer* (Co-PI with R. Deshaies and K.Sakamoto at CalTech)
2000 **NIH** Diabetes Endocrinology Research Center (DERC) Pilot Project
2001 **NIH R21** DK06340-04 *Pancreatic Stem Cell Induction by Small Molecules*
2002 **NIH T32** GM067543 *Predoctoral Training at the Interface of Chemistry and Biology*
2003 **NIH R01** AI055914 *Anti-inflammatory Natural Product Mode of Action Studies*

State

1996 **Donaghue Foundation** New Investigator Grant Award (Support for laboratory research for three years) *Angiogenesis: The Intersection of Cardiovascular and Tumor Biology*

PRIVATE SECTOR FUNDING SUPPORT

PharmaMar, s.a.
Ancile Pharmaceuticals
Novartis Pharmaceuticals
Pfizer Corporation
Ambit, Inc.

SERVICE

Federal

- National Cancer Institute Intramural Review Panel, Medicinal Chemistry, May 2001
- Ad hoc Study Section Member, Biorganic Nat. Product Study Section, NIH, July 2001
- ZRG1 SSS-H 92S, Drug Development for Cancer, NIH Study Section, July, 2003
- ZRG1 SSS-1 12B SBIR/STTR Cancer Diagnostic and Treatment Study Section, Feb, 2004
- ZNA1 SRB-E (13) High Throughput Molecular Screening Assay Dev., Aug, 2004
- Ad hoc Study Section Member, Biorganic Nat. Product,Study Section, NIH, Oct. 2004
- ZRG1 NCF (09) Study Section, NIH, March 2005
- Ad hoc Member, Drug Discovery and Molecular Pharmacology Study Section (DMP), NIH, November 2005

University

- Co-founder, Chemical Biology Seminar Series, 1996-
- College Freshman Faculty Advisor, 1996-
- Organizer, Chemical Biology Symposia, 1998-2003
- Member, University Committee on the Economic Status of the Faculty, 1998-1999
- Member, College Admissions Science & Engineering Policy Committee, 1998
- Participating Faculty Member, STARS Program for under-represented minorities in the sciences
- Member, MBB Junior Faculty Search Committee, 1999-2000
- Round Table Participant, Yale University 1999 Re-accreditation Site Visit (New England Assoc. of Schools and Colleges)
- Member, Advisory Board for the Office of Graduate Career Services, 2000-2003

- Co-Organizer, Yale Corporate Partners Program for Science Hill, 2000-
- Member, Advisory Committee on Yale College Admissions and Fin. Aid Policy, 2002-
- Member, Committee on Cooperative Research, 2005-2006

Department

- Member, Undergraduate Affairs Committee, 1997-1998
- Member, Departmental Development Committee, 1997-2001 (Chairman, 1998)
- Member, Junior Faculty Search Committee, 1997-2001
- Member, Graduate Student Affairs Committee, 1998-1999; 2001-
- Member, New Building Committee, 2000-
- Director of Graduate Admissions, 2001-

Other

- Member, External Review Committee for U. Texas-Southwestern Medical Center Chemical Biology Program
- Member, Graduate Student Thesis Examination Committee, Dept. of Chemistry and Chemical Biology, Harvard University

CONSULTANCIES

1997- 2000	Pfizer Corporation (Drug Pfinder Program)
1998- 2002	Novartis Pharmaceutical Corporation
1998- 2002	Ancile Pharmaceuticals
2000- 2002	Osteoscreen
2001- 2002	Boehringer-Ingelheim
2001- 2003	Morphochem
2004	ChemGenomics, Inc.
2003-	Proteolix, Inc./(*co-founder*)

PROFESSIONAL PERSONNEL TRAINED

Graduate Students

P. Gupta (Mol.Biophys.Biochem. Dept.) (recipient of NSF Pre-doctoral Fellowship)
L. Meng
J. Yeh
J. Vervoort
B. Kwok
C. Brdlik (Genetics Dept.)
B. Koh (M.D./Ph.D. Program) (recipient of a NIH Cancer Education Grant)
B. Shotwell (joint with John Wood -Chemistry) (recipient of NSF Pre-doctoral Fellowship and ACS Medicinal Chemistry Fellowship)
J. Schneekloth (recipient of ACS Medicinal Chemistry Fellowship)
L. Campbell
A. Smith

Additional Graduate Rotation Students: 24 *Graduate Student Committees:* 19

Medical Students

J. Abraham - recipient of a Research Fellowship from The Angiogenesis Foundation
- recipient of the Etta S. Chidsey Award in Cancer Research (Yale School of Medicine)

Postdoctoral Associates Trained:

N. Sin - recipient of Sessel Anonymous Postdoctoral Fellowship (Yale University)
M. Elofsson - recipient of Swedish Research Council Postdoctoral Fellowship
J. Wen
J. Thakkar
U. Splittgerber - recipient of German Chemical Industry Association Fellowship
D. Bilodeau - recipient of a Quebec Research Council Fellowship
K. Kim
L. Willer
R. Mohan
S. Hu
J. Myung - recipient of Anderson Postdoctoral Fellowship (Yale University)
M. Ndubuisi - recipient of UNCF: Pfizer Postdoctoral Fellowship
S. Leuenroth - recipient of an American Cancer Society Postdoctoral Fellowship
S. Lee
J. Hines - recipient of Leukemia and Lymphoma Society Postdoctoral Fellowship
A. Mandal
Y. Zhang
E. Ami
R. Ju
W. Zhang
J. Gough
K. Kuramochi -recipient of the Uehara Memorial Foundation Postdoctoral Fellowship
M. Pucheault- recipient of a HFSP Postdoctoral Fellowship
P. Cirone
R. Peterson
A. Petri – recipient of a German Research Foundation (DFG) Postdoctoral Fellowship

Undergraduates Trained in Laboratory Research Projects: 19

MCDB Dept.: M. Barnett, M. Henry, D. Oppenheim, E. Schroeder, J. Adams, K. Harmon, A. Maldonado, E. Bigger, A. Chen, M. Matyskiela, Christina Agapathis; **MBB Dept.**: S. Denenberg, R. Woodruff, S. Lo, M. Koldobskiy; **Chemistry Dept.:** J. Sanders, N. Okeke, J. Emerson; **Southern Connecticut State University:** H. Auk, R. Goetsch.

Honors: K. Harmon - NIH Minority Scholarship Award (declined), Bouchet Scholar
D. Oppenheim- Belknap Prize for Best Undergraduate Research Project
S. Lo- Yale Science and Engineering Association Undergrad Research Prize

- Mellon Undergraduate Research Grant, Yale University
- Summer Fellowship, Gatorade Company and Lecture Program at Yale
- HHMI Summer Undergraduate Research Fellowship

N. Okeke - Bouchet Scholar, Yale University

M. Koldobskiy - Richter Summer Research Fellowship, Davenport College, Yale University

J. Sanders- HHMI Summer Undergraduate Research Fellowship

M. Barnett- HHMI Summer Undergraduate Research Fellowship

TOTAL PUBLICATIONS: 60 [53 published; 5 submitted; 2 in press]: total includes 11 review articles (denoted ^); 5 book chapters (denoted #), 42 research papers of which 7 provoked journal commentaries (denoted *), and 3 papers featured as cover art (denoted ‡).

(1) **1989** Alcorta, D., C.M. Crews, L.J. Sweet, L. Bankston, S.W. Jones, and R.L. Erikson. Molecular characterization of chicken and mouse homologs of the Xenopus ribosomal S6 kinase, Rsk. *Mol. Cell. Biol.*, **9**:3850-3859.

(2) **1991** Crews, C.M., A.A. Alessandrini, and R.L. Erikson. The Erk1 gene product is a serine/threonine protein kinase that has the potential to phosphorylate tyrosine. *Proc. Natl. Acad. Sci. USA*, **88**:8845-8849.

* *subject of commentary in 'The Scientist'*

(3) **1992** Crews, C.M., A.A. Alessandrini, and R.L. Erikson. The primary structure of MEK, a protein kinase that phosphorylates and activates the ERK gene product. *Science*, **258**:478-480.

* *subject of commentary in 'Journal of NIH Research'*

(4) Crews, C.M. and R.L. Erikson. Purification of a protein tyrosine/threonine kinase that phosphorylates and activates the Erk1 gene product: Relationship to the yeast gene *byr1*. *Proc. Natl. Acad. Sci. USA*, **89**:8205-8209.

(5) Alessandrini, A.A., C.M. Crews, and R.L. Erikson. Phorbol ester stimulates a protein tyrosine/threonine kinase that phosphorylates and activates the Erk1 gene product. *Proc. Natl. Acad. Sci. USA*, **89**:8200-8204.

(6) Calvo, V., C.M. Crews, T.A. Vik, and B.E. Bierer. Interleukin 2 stimulation of p70 S6 kinase is inhibited by the immunosuppressant rapamycin. *Proc. Natl. Acad. Sci. USA*, **89**:7571-7575.

(7)^ Crews, C.M., A.A. Alessandrini, and R.L. Erikson. Erks: Their fifteen minutes has arrived. *Cell Growth and Differentiation*, **3**:135-142.

(8) **1993**^ Crews, C.M. and R.L. Erikson. Extracellular signals and reversible protein phosphorylation: What to MEK of it all. *Cell.* **74**:215-217.

(9) Macdonald, S.G., C.M. Crews, L. Wu, J. Driller, R. Clark, R.L. Erikson, F. McCormick. Reconstitution of the raf-1-MEK-ERK signal transduction pathway *in vitro. Mol. Cell. Biol.*, **13**:6615-6620.

(10) Huang, W., A. A. Alessandrini, C.M. Crews, R.L. Erikson. Raf-1 forms a stable complex with MEK1 and activates MEK1 by serine phosphorylation. *Proc. Natl. Acad. Sci. USA*, **90**:10947-10951.

(11) Brott, B.K., Alessandrini, A., Largaespada, D. A., Copeland, N. G., Jenkins, N. A., Crews, C.M. and R.L. Erikson. MEK2 is a kinase related to MEK1 and is differentially expressed in murine tissues. *Cell Growth Differ.* **4**(11):921-9.

(12) **1994** Crews, C.M., J.L. Collins, W.S. Lane, M.L. Snapper, and S.L. Schreiber. GTP-dependent binding of the antiproliferative agent didemnin to elongation factor 1α. *J.Biol.Chem.* **269**:15411-15414.

* *subject of 'Chemistry and Engineering News' (CEN) commentary*

(13) **1995#** Erikson, R.L., A.A. Alessandrini , C.M. Crews. Mek1, Mapk/Erk Kinase The Protein Kinase Facts Book p.275-277.

- Assumed Independent Research Program at Yale University -

(14) **1996** Crews, C.M., W.S. Lane, and S.L. Schreiber. Didemnin binds to the palmitoyl protein thioesterase responsible for infantile neuronal ceroid lipofuscinosis *Proc. Natl. Sci. USA*, **93**:4316-4319.

(15)^ Crews, C.M. Deciphering Isozyme Function: Exploring Cell Biology with Chemistry in the Post-Genomic Era *Chemistry and Biology* **3**:961-965.

(16) **1997** Sin, N., L.Meng, M.Q.W.Wang, J.J.Wen, W.G.Bornmann, and C.M. Crews. Fumagillin covalently binds and inhibits methionine aminopeptidase, MetAP-2. *Proc. Natl. Acad. Sci. USA*, **94**:6099-6103.

* *subject of commentaries in Chemistry and Engineering News (CEN), Chemistry & Biology, Pharmacia (published by the Pharmaceutical Society of Japan)*

(17) **1998** Wen, J.J., and C.M. Crews. Towards the semi-synthesis of Didemnin M. Solution and solid phase synthesis of a pseudotetrapeptide: pGlu-Glnψ[COO]Ala-Pro-OH. *Tetrahedron Letters*, **39** (8):779-782.

(18)^ Elofsson, M. and C.M.Crews. Tightening the Nuts and Bolts. *Trends in Biotechnology*,**16**:147-149.

(19) Wen, J.J., and C.M. Crews. Synthesis of 9-Fluorenylmethoxycarbonyl Protected Amino Aldehydes. *Tetrahedron Asymmetry,* **9** (11): 1855-1858.

(20) Sin, N., L. Meng, H.Auth, and C.M. Crews. Eponemycin Analogs: Syntheses and use as probes of angiogenesis. *Bioorganic & Med.Chem.***6**:1209-1217

(21) Meng, L., N.Sin, and C.M. Crews. The antiproliferative agent, didemnin B, uncompetitively inhibits palmitoyl protein thioesterase. *Biochemistry* **37**(29):10488-10492.

(22) Liu, S., J. Widom, C.W. Kemp, C.M. Crews, and J. Clardy. Atomic Structure of Human Methionine Aminopeptidase 2 Complexed with the Angiogenesis Inhibitor Fumagillin. *Science* **282**:1324-1327

* *subject of 'Chemistry and Engineering News' (CEN) and 'Drug Discovery and Development' commentaries*

(23) **1999** Meng, L., Kwok, B., N. Sin, and C.M. Crews. Eponemycin Exerts its Antitumor Effect through Inhibition of Proteasome Function. *Cancer Research,* **59**: 2798-2801.

(24) ^ Crews, C.M. and U. Splittgerber. Chemical Genetics: Exploring and Controlling Cellular Processes with Chemical Probes. *Trends in Biochemical Sciences,* **24**:317-320.

(25) Sin, N., Kim, K., Elofsson, M., Meng, L., Auth, H. Kwok, B.H.B., and C.M. Crews. Total Synthesis of the Potent Proteasome Inhibitor Epoxomicin: A Potential Tool for Understanding Proteasome Biology. *Bioorganic & Med. Chem. Letters,* **9**:2283-2288.

(26) Meng, L., Mohan, R., Kwok, B.H.K., Elofsson, M., N. Sin and C.M. Crews. Epoxomicin, a Potent and Selective Proteasome Inhibitor exhibits *in vivo* Anti-inflammatory Activity. *Proc. Natl. Acad. Sci. USA,* **96**:10403-10408.

(27)‡ Elofsson, M., Splittgerber, U., Myung, J., and C.M. Crews. Towards Subunit-specific Proteasome Inhibitors: Synthesis and Evaluation of Peptide α'β'-epoxyketones. *Chemistry & Biology,* **6**:811-822.

* *subject of 'Chemistry and Engineering News' (CEN)*

(28) Kim, K., Myung, J., Sin, N., and C.M. Crews. Proteasome Inhibition by the Natural Products Eponemycin and Epoxomicin: Insights into Specificity and Potency. *Bioorg. Med. Chem. Lett.* **9**:3335-3340.

(29) **2000** Groll, M., Kim, K., Kairies, N., R. Huber, and C.M. Crews. The Molecular Basis for the Selectivity of an α', β'-epoxyketone Proteasome Inhibitor revealed by Crystal Structural Analysis of an Epoxomicin:20S Proteasome Complex. *J.Am.Chem.Soc.,* **122**:1237-1238.

* *subject of 'Chemistry and Engineering News' (CEN)*

(30) ^ C.M. Crews and Mohan, R. Small Molecule-based Manipulation of the Cell Cycle. *Curr. Opin. Chem. Biol.* **4**:47-53.

(31) Schwarz, K., de Giuli, R., Schmidtke, G., Kostka, S., van den Broek, M., Kim, K., C.M. Crews, Kraft, R., and M. Groettrup. The selective proteasome inhibitors lactacystin and epoxomicin can be used to either up- or downregulate antigen presentation at non-toxic doses *J. Immunology,* **164**(12):6147-57.

(32) Shotwell, J.B., Hu, S., Medina, E., Abe, M., Cole, R., Crews, C.M., and J.L.Wood. Efficient stereoselective synthesis of isopanepoxydone and panepoxydone: A re-assignment of relative stereochemistry. *Tetrahedron Letters,* **41**:9639-9643.

(33) Yeh, J., Mohan, R., and C.M. Crews. The Antiangiogenic Agent TNP-470 requires p53 and $p21^{CIP/WAF}$ for Endothelial Cell Growth Arrest. *Proc. Natl. Acad. Sci. USA,***97**:12782-12787

(34) **2001** Princiotta, M.F., U. Schubert, I. Bacik, J. R. Bennink, J. Myung, C.M. Crews, and J. W. Yewdell. Cells adapted to the proteasome inhibitor 4-hydroxy- 5-iodo-3-nitrophenylacetyl-Leu-Leu-leucinal-vinyl sulfone require enzymatically active proteasomes for continued survival. *Proc. Natl. Acad. Sci. USA,* **98**(2):513-518.

(35) Myung, J., Kim, K., Lindsten, K.K., Dantuma, N.P., and C.M. Crews. Lack of Proteasome Active Site Allostery as Revealed by Subunit-Specific Inhibitors. *Molecular Cell,* 7(2):411-420.

(36)‡ ^ Myung, J., Kim, K., C.M. Crews. The Ubiquitin-proteasome Pathway and Proteasome Inhibitors. *Medicinal Research Reviews,* **21**:245-273.

(37)‡ Kwok H.B., Koh, B., Ndubuisi, M., Elofsson, M., and C.M. Crews. The Anti-inflammatory Agent Parthenolide from the Medicinal Herb Feverfew Directly Binds to and Inhibits I□B Kinase. *Chemistry & Biology* **8**(8):759-66.

(38) Sakamoto, K.M., Kim, K.B., Kumagai ,A., Mercurio, F., C.M. Crews, and R.J. Deshaies. Protacs: Chimeric Molecules that Target Proteins to the SCF Complex for Ubiquitination and Degradation, *Proc. Natl. Acad. Sci. USA* **98**:8554-8559.

(39) **2002** Ndubuisi, M., Kwok, B., Vervoort, J., Elofsson, M. and C.M. Crews. Characterization of p34, a specific *p*-nitrophenyl phosphatase from EL4 cells *Biochemistry,* 41(24):7841-8.

(40) Shotwell, J.B., Koh, B., Ndubuisi, M., Choi, H.W., Medina, E., Wood, J.L., C.M. Crews Novel Inhibitors of NF-κB Signalling: Design and Synthesis of a Biotinylated Isopanepoxydone Affinity Reagent. *Bioorganic and Medicinal Chemistry Letters* **12** (23): 3463-3466

(41) J. B. Shotwell, E.S. Krygowski, J. Hines, B. Koh, E.W. D. Huntsman, H. W. Choi, J.S. Schneekloth Jr., J. L. Wood, and C.M. Crews Total Synthesis of Luminacin D *Organic Letters*, **5**;4(18):3087-9

(42) ^ Koh, B. and C.M. Crews Chemical Genetics: A Small Molecule Approach to Neurobiology *Neuron* **14;36**(4):563-6.

(43) **2003#** C.M. Crews, and K.B. Kim Natural and Synthetic Inhibitors of the Proteasome Proteasome Inhibitors in Cancer Therapy, (J. Adams, editor)

(44) # C.M. Crews and Shotwell, J.B. Small Molecule Inhibitors of the Cell Cycle *Prog Cell Cycle Res.* **5**:125-33

(45) Garrett, I.R., Gutierrez, G., Rossini, G., Zhao, M., Kim, K.B., Hu, S., C.M. Crews, and G.R. Mundy Selective inhibitors of the osteoblast proteasome stimulate bone formation *in vivo* and i*n vitro. J Clin Invest.* **111**(11):1771-82.

(46) Z-Q. Yang, B. Kwok, S. Lin, M. Koldobskiy, C.M. Crews, and S. J. Danishefsky Simplified Synthetic TMC-95A/B Analogues Retain the Potency of Proteasome Inhibition *ChemBioChem* **4**:508-513.

(47)^ Yeh, J. and C.M. Crews Chemical Genetics: Adding to the Developmental Biology Toolbox *Developmental Cell* **5**(1):11-19.

(48)^ C.M. Crews Feeding the Machine: Mechanisms of Proteasome-catalyzed Degradation of Ubiquinated Proteins *Curr Opin in Chemical Biology*,**7**(5):534-9.

(49) Sakamoto, K. M., K. Kim, R. Verma, A. Ransick, B. Stein, C. M. Crews, and R. J. Deshaies Development of Protacs to Target Cancer -Promoting Proteins for Ubiquitination and Degradation *Mol Cell Proteomics* **2**(12):1350-1358.

(50) **2004** Brdlik, C., and C.M. Crews A Single Amino Acid Residue Defines Inhibitor Specificity for the Methionine Aminopeptidase Family. *J.Biol.Chem.* **279**:9475-80.

(51) Schneekloth, Jr., J.S., F. Fonseca, M. Koldobskiy, A. Mandal, R. Deshaies, K. Sakamoto, and C. M. Crews Chemical Genetic Control of Protein Levels: Selective *in vivo* Targeted Degradation *JACS* **126**(12):3748-54

(52) Lin S, Yang ZQ, Kwok BH, Koldobskiy M, Crews CM, Danishefsky SJ.

Total synthesis of TMC-95A and -B via a new reaction leading to Z-enamides. Some preliminary findings as to SAR. *JACS.* **126**(20):6347-55.

(53) Zhang, Y., J.R. Yeh, , A. Mara, R.Ju, J. Hines, W. Zhang, D. Slusarski, S. Holley, and C. M. Crews Chemical and Genetic Inhibition of Methionine Aminopeptidase-2 Links Non-canonical Wnt Signaling and Angiogenesis (*submitted*)

(54) **2005**^ Schneekloth, J., C.M. Crews Chemical Approaches to Controlling Intracellular Protein Degradation *ChemBioChem* **6**(1):40-6.

(55) # Kim, K.B., F. Fonseca, C.M. Crews Development and Characterization of Proteasome Inhibitors Methods in Enzymology (*in press*)

(56) # Gough, J.D. and C.M. Crews Probing Protein Function with small molecules. *Ernst Schering Research Foundation* Chemical Genomics *Workshop Proceedings.* Springer-Verlag *(in press)*

(57) Mandal, A.K., J. S. Schneekloth, Jr., and C.M. Crews Stereoselective Assembly of a 1,3-Diene via Coupling between an Allenic Acetate and a (B)-alkylborane: Synthetic Studies on Amphidinolide B1. *Organic Letters,* 7(17):3645-8

(58) Mandal, A., J. Hines, and C.M.Crews Developing Microcolin A Analogues as Biological Probes *Bioorg. Med.Chem Letters* **15**(18):4043-7

(59) Leuenroth, S, and C.M. Crews Studies on Calcium Dependence Reveal Multiple Modes of Action for Triptolide Chem Biol. 2005.Dec;12(12):1259-68.

(60) **2006** Mandal AK, Schneekloth JS Jr, Kuramochi K, Crews CM. Synthetic studies on amphidinolide B1. *Org Lett.* 2006 Feb 2;**8**(3):427-30.

INVITED LECTURES (TOTAL OF 121)

1994

- Gordon Conference on "Marine Natural Products", Ventura, CA, (February, 1994)

1995

- Pharma Mar, s.a., Madrid, Spain (July 1995)
- Yale University, Pharmacology Department (December 1995)

1996

- Pharmacopeia, Inc. (April 1996)
- Gordon Conference on "Natural Products", Henniker, New Hampshire, (July 1996)

- University of Connecticut, Department of Medicinal Chemistry, (November 1996)

1997

- Curagen Corporation (February 1997)
- NCI US-Japan Joint Seminar on Exp. Antitumor Therapeuitics, Maui, Hawaii (March 1997)
- Bayer Corporation (April 1997)
- Neurogen Corporation (April 1997)
- Abbott Laboratories (June 1997)
- Pfizer Pharmaceuticals (July 1997)
- Vertex Pharmaceuticals (July 1997)
- CaPCURE Scientific Retreat, Lake Tahoe, (September 1997)
- IBC Conference on Combi. Chem., *Session Chairman*, San Diego (October 1997)
- Novartis Pharmaceuticals, (October 1997)
- IBC Conference on Proteomics, Boston (November 1997)
- University of Texas at Southwestern, Dallas, Biochemistry Dept. (December 1997)

1998

- Yale University, Pharmacology Department (February 1998)
- U.S. Surgical Corporation (March 1998)
- National Cancer Institute, Frederick, MD (March 1998)
- American Chemical Society National Meeting (Med. Chemistry Section), Dallas (April 1998)
- Yale Chemical Biology Symposium (April 1998)
- Yale Cancer Center Grand Rounds (May 1998)
- Gordon Conference on 'Natural Products", Henniker, New Hampshire (July 1998)
- CaPCURE Scientific Retreat, Lake Tahoe (September 1998)
- ProScript, Inc., Cambridge (October 1998)
- PharmaMar, s.a., Cambridge, MA (October 1998)

1999

- Novartis Pharmaceuticals, Summit, New Jersey (February 1999)
- 3rd Workshop on the Proteasome, Universite de Clermont-Ferrand, France (March 1999)
- University of Texas at Southwestern, Dallas, Biochemistry Department (May 1999)
- Gordon Conference on Bioorganic Chemistry, Andover, New Hampshire, (June 1999)
- FASEB Meeting on Ubiquitin, Saxtons River, Vermont, (August 1999)
- Sphinx Pharmaceuticals, Cambridge , MA (September 1999)
- Swedish Pharmaceutical Society Conference on Medicinal Chemistry, Stockholm, (October 1999)
- Karolinska Insitute, Microbiology and Tumor Biology Center, Stockholm, (October 1999)
- Biomedical Center, Uppsala, (October 1999)
- University of Umeå, Department of Biochemistry, Umeå, Sweden (October 1999)

- Syracuse University, Department of Biology, Syracuse (October 1999)
- Chiron Corporation, Emeryville, California (October 1999)
- University of California at San Francisco, Cellular and Molecular Pharmacology (October 1999)
- University of Rochester, Department of Chemistry (November 1999)
- Hunter College, CUNY, Department of Biology (November 1999)

2000

- University of Texas Health Science Center, San Antonio, TX (January 2000)
- MRC, Laboratory of Molecular Biology, Cambridge, UK (January 2000)
- Kings College London, UK (January 2000)
- Notre Dame University, Walther Cancer Research Center (February 2000)
- American Chemical Society National Meeting, San Francisco (March 2000)
- University of Delaware, Department of Chemistry (March 2000)
- Bristol-Myers Squibb, (April 2000)
- Yale University, Yale Science Forum (April 2000)
- Genentech, South San Francisco, CA (May 2000)
- Tularik, South San Francisco, CA (May 2000)
- Boehringer Ingelheim, Ridgefield, CT (June 2000)
- Pharmacia/UpJohn, St.Louis, MO (August 2000)
- Wesleyan University, Chemistry/Biochemistry Seminar Series (November 2000)
- Duke University, Biochemistry Department (November 2000)
- University of Pennsylvania, Chemistry Department (November 2000)
- American Chemical Society PacifiChem2000 Meeting, Honolulu (December 2000)

2001

- California Institute of Technology, Division of Biochemistry (January 2001)
- University of Mass. Medical Center, Biochem. & Mol. Pharm. (February 2001)
- New York Medical College, Biochemistry Department (February2001)
- Chemical Genomics Symp., Korean Chem. Society Meeting, Seoul (April 2001)
- Chemical Genomics Minisymposium, Pohang University, Pohang, Republic of Korea (April 2001)
- Kyoto Pharmaceutical University, Dept. of Med. Chem (April 2001)
- Science University of Tokyo, Faculty of Pharmaceutical Sciences (April 2001)
- Sankyo Corporation, Tokyo (April 2001)
- EntreMed, Inc., Rockville, MD (May 2001)
- Gordon Conference on Exp. Chemotherapy, Session Chairman, (July 2001)
- Chemical Biology Mini-symposium, Hong Kong University, (July 2001)
- American Chemical Society National Meeting (Med. Chemistry Section), Chicago (August 2001)
- British Assoc. for Cancer Research Conference *'Forging an Alliance between Genomics, Proteomics and Chemical Biology to Accelerate Cancer Drug Discovery'* London (September 2001)
- MorphoChem, Inc. (November 2001)

- National Research Council of Canada, Steacie Institute for Molecular Sciences, Chemical Biology Program, (November 2001)
- American Society for Cell Biology Annual Meeting, Co-Chair of Minisymposium on *Chemical Approaches to Cell Biology*, Washington, D.C. (December 2001)

2002

- The Association for Research in Otolaryngology Midwinter Meeting, *Signal Transduction for the 21st Century* Symposium, St. Petersburg, Florida (Jan. 2002)
- University of Illinois, Department of Chemistry, (April 2002)
- The Vanderbilt Conferences, *Proteomics: The Next Grand Biological Challenge*, Nashville, Tennessee (May 2002)
- New York Academy of Sciences, Chemical Genetics Symposium, New York City, (October 2002)
- New York University, Chemistry Department, New York City (December 2002)

2003

- Massachusetts Institute of Technology, Chemistry Department (February 2003)
- Japan Society for Bioscience, Biotechnology and Agrochemistry, Chemistry and Biology Symposium, Plenary Lecture, Fujisawa City (March 2003)
- American Society for Biochemistry and Molecular Biology, National Meeting; Symp. on Protein Synthesis and Degradation, San Diego, California (April 2003)
- University of Kentucky, Department of Pharmacology and Chemistry (May 2003)
- Cornell University, Guest Lecturer in Chemical Biology Course (July 2003)
- American Assoc. For Cancer Research, Chemgenomics Symposium (Session Organizer), Washington, D.C. (July 2003)
- IUPAC/CSC, Symposium on Organic Synthesis and Chemical Biology, Ottawa, (August 2003)
- Korea Institute of Science and Technology (KIST), Chemical Genomics Symposium, Seoul, (August 2003)
- IBC Chemical Genomics Symposium, Boston (October 2003)
- Massachusetts General Hospital, Cardiovascular Research Center, (October 2003)
- National Cancer Institute, NIH, Molecular Targets for Cancer Drug Discovery Workshop, (October 2003)
- U. Pennsylvania, Symposium on 'Inhibitors of Protein-Protein Interactions', Depts. of Biochem.& Biophysics and the Department of Chemistry, (Nov. 2003)
- Merck-Frosst Canada, Ltd., Montreal (November 2003)
- Yale University, Vascular Biology and Transplantation Program Retreat, (December 2003)
- American Society of Cell Biology (ASCB) Annual Meeting, Chemistry/Biology Interface Mini-symposium, San Francisco (December 2003)

2004

- NIH Chemical Genomics Conference, Bethesda (March 2004)
- Emory University, Departments of Pharmacology and Chemistry, (March 2004)

- Memorial Sloan Kettering Cancer Center, Molecular Pharmacology and Chemistry Seminar Series, (May 2004)
- EMBL, "Chemical Approaches to the Study of Biology" Symposium, Heidelberg (June 2004)
- Institut de Chimie des Substances Naturelles 9th Symposium 'Cancer: Targets, Molecules, and Therapies', Plenary Lecture, Gif-sur-Yvette, France (June 2004)
- University of Chicago, Dept of Molecular Genetics and Cell Biology (Nov. 2004)
- Society of Industrial Microbiology GMBIM/BMP Conference, San Diego (November 2004)
- German ChemBioNet Symposium, Frankfurt (December 2004)

2005

- Princeton University, Chemistry Department, (February 2005)
- U. Illinois at Chicago, Chemistry Department, (February 2005)
- Vertex Pharmaceutics, Cambridge, MA (April 2005)
- Ernst Schering Research Foundation Workshop, 'Chemical Genomics: Small Molecule Probes to Study Cellular Function', Berlin, (April 2005)
- Institut Pasteur, Department of Structural Biology and Chemistry, Paris (April 2005)
- Roswell Cancer Center, Buffalo, NY (May 2005)
- Case Western Reserve University, Cleveland (May 2005)
- Tissue Repair and Regeneration Gordon Conf., Colby-Sawyer, NH (June 2005)
- European Life Sciences Organization (ELSO) Meeting, Mini-Symposium on Chemical Biology, Dresden (September 2005)
- Max Planck Institute of Molecular Cell Biology and Genetics, Dresden (Sept. 2005)
- New York Academy of Sciences Symposium on Regenerative Medicine, New York (September 2005)
- U. Illinois, Chemical Biology Seminar Series, Champaign-Urbanna, (October 2005)
- Gilead Pharmaceuticals, Foster City, CA (November 2005)
- UCSF, Chemistry and Chemical Biology Program, San Francisco (November 2005)
- Johnson&Johnson Pharmaceuticals, Spring House, PA (November 2005)
- Novartis, Cambridge, MA (December 2005)

2006

- Bristol Myers-Squibb, Wallingford, CT (January 2006)
- NIH, Chemistry Seminar Series, Bethesda, MD (January 2006)
- American Chemical Society National Meeting, Atlanta (March 2006)
- Ohio State Chemistry/Biology Interface Symposium, Columbus (May 2006)

PATENTS

'Enzyme Inhibition'
Patent US 6,831,099 B1

'Protechials (Proteolysis-Targeting Chimeric Pharmaceutical)' (Collaboration with R. Deshaies, CalTech)
Provisional Patent submitted

LABORATORY WEBSITE: www.yale.edu/crews